CLAIMS

We claim:

1. A method for increasing the level of a therapeutic gene product in a subject, the method comprising administering to said subject a viral vector comprising a therapeutic nucleic acid encoding said therapeutic gene product and an agent that modulates Kupffer cell function in said subject.

2. The method according to claim 1, wherein said viral vector is an adenovirus vector.

3. The method according to claim 1, wherein said agent modulates Kupffer cell function by lowering levels of Kupffer cells in said subject.

4. The method according to claim 3, wherein said agent comprises doxorubicin.

5. The method according to claim 4, wherein said doxorubicin is provided in a liposome.

6. The method according to claim 1, wherein said agent modulates uptake of said viral vector by a Kupffer cell in said subject.

7. The method according to claim 1, wherein said Kupffer cell function is uptake of a viral vector comprising said therapeutic nucleic acid.

8. The method according to claim 1, wherein said agent is a viral vector that does not comprise said therapeutic nucleic acid.

9. The method according to claim 1, wherein said agent is an adenovirus vector that does not comprise said therapeutic nucleic acid.

10. The method according to claim 1, wherein said agent is administered prior to administering said viral vector.

11. The method according to claim 10, wherein said agent is administered less than 24 hours prior to administering said viral vector.

12. The method according to claim 10, wherein said agent is administered less than 1 hour prior to administering said viral vector.

13. The method of claim 10, wherein said agent is administered less than five minutes prior to administering said viral vector.

14. The method according to claim 1, wherein said agent is administered concurrently with the viral vector.

15. The method according to claim 1, wherein said agent is a particle sufficient for phagocytosis.

16. The method according to claim 15, wherein said particle has a diameter of about 10 nm to about 1000 nm.

17. The method according to claim 1, wherein said subject is a rodent.

18. The method according to claim 1, wherein said subject is a primate.

19. The method according to claim 18, wherein said primate is a human.

20. The method according to claim 1, wherein said viral vector is administered by a route selected from the group consisting of oral administration, nasal administration, parenteral administration, transdermal administration, topical administration, intraocular administration, intrabronchial, intraperitoneal administration, direct injection into cells, tissue, organ or tumor, intravenous administration, subcutaneous administration, and intramuscular delivery.

21. The method according to claim 1, wherein said agent is administered by a route selected from the group consisting of oral administration, nasal administration, parenteral administration, transdermal administration, topical administration, intraocular administration, intrabronchial, intraperitoneal administration, direct injection into cells, tissue, organ or tumor, intravenous administration, subcutaneous administration, and intramuscular delivery.

22. The method according to claim 20, wherein said agent is administered by a route selected from the group consisting of oral administration, nasal administration, parenteral administration, transdermal administration, topical administration, intraocular administration, intrabronchial, intraperitoneal administration, direct injection into cells, tissue, organ or tumor, intravenous administration, subcutaneous administration, and intramuscular delivery.

23. The method according to claim 1, wherein said viral vector is a replication-defective viral vector.

24. The method according to claim 8, wherein said agent is a replication defective viral vector.

25. A method for increasing levels of a therapeutic gene product in a hepatocyte cell population, the method comprising contacting said hepatocyte cell population with a viral vector comprising a therapeutic nucleic acid encoding said therapeutic gene product and an agent that modulates Kupffer cell function in said subject.

26. The method according to claim 25, wherein the Kupffer cell function being modified is uptake of the agent.

27. A method of modulating toxicity associated with a virally encoded transgene, the method comprising administering to a subject an agent that modulates Kupffer cell level or Kupffer cell function in said subject.

28. The method according to claim 27, wherein said agent is administered prior to administration of a therapeutic nucleic acid encoding a therapeutic gene product.

29. The method according to claim 27, wherein said toxicity is hepatotoxicity.

30. A method for modulating delivery of a virally encoded transgene to a subject, the method comprising:

(a) identifying a dosage inflection point of a virus containing said virally encoded transgene in said subject;

(b) comparing said inflection point to levels of a product of said virally encoded transgene in said subject; and

(c) adjusting if necessary the dose of virus administered to said subject, thereby modulating dosage of said virally encoded transgene.

31. A method for modulating delivery of a virally encoded transgene to a subject, the method comprising:

(a) identifying a first dosage inflection point of a first virus not containing said encoded transgene in said subject, thereby saturating a Kupffer cell function;

(b) identifying a second dosage inflection point of a second virus containing said virally encoded transgene in said subject, wherein the dosage curve is non-linear;

(c) comparing said second inflection point to levels of a product of said virally encoded transgene in said subject; and

(d) adjusting if necessary the doses of the first virus and second virus administered to said subject, thereby modulating dosage of said virally encoded transgene.

32. A pharmaceutical composition comprising a viral nucleic acid encoding a therapeutic gene product,

an agent that modulates Kupffer cell function, and a pharmaceutically acceptable carrier.

33. The pharmaceutical composition according to claim 32, wherein said viral nucleic acid is provided in a viral particle.